REMARKS

Applicant respectfully requests entry of the Amendment and reconsideration of the claims. Claims 105, 115, and 123 have been amended. Applicant currently amends claim 123 to correct an obvious typographical error. Applicants submit that the claims as amended are supported throughout the specification including at page 59, lines 23-25; page 100, lines 5-15; and page 107, lines 18-28.

Claims 105-107, 109-111, and 113-128 are pending. Claims 1-7, 9-12, 15-24, 29-34, 36-40, 42, 44-46, 48-54, 59-66, 68-74, 76, 81-85, 90-96, 98-99, 108, 112, and 129-130 are withdrawn. Applicants request rejoinder of these claims after notice of allowable subject matter of claim 105.

Priority

The Examiner objects to the claim for the benefit of priority and contends that provisional applications 60/441,059 filed 1/16/2003, 60/488,610 filed July 18, 2003, and 60/510,314 filed October 8, 2003 do not provide support for a CDRH3-phage coat fusion protein comprising a "N terminal portion of about 1 to 4 amino acids in which some or all amino acid positions are structural" and a "C terminal portion of about 1 to 6 amino acids in which some or all amino acid positions are structural". The Examiner further asserts that a fusion protein comprising at least a portion of a phage coat protein is not supported in the earlier applications as well. Applicants respectfully disagree with the Examiner and request acknowledgement of the claim for priority of the currently pending claims. We further understand the examiner's rejection to be based on a 112 rejection. Applicants traverse this rejection.

The written description requirement requires that Applicants' specification must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991). A written description of an invention involving a chemical genus requires a precise definition, such as by structure, formula ... of the claimed subject matter sufficient to distinguish it from other materials. Univ. of California v. Eli Lilly and Co., 43 USPQ2d 1398. 1405 (Fed. Cir. 1997) (emphasis added). Since one skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass, such a formula is

normally an adequate description of the claimed invention. Id. at 1406 (emphasis added). there is a "strong presumption" that an adequate written description of the claimed invention is present when the application is filed. In re Wertheim, 191 USPQ 90,97 (CCPA 1976). Compliance with the written description requirement does not require an applicant to describe exactly the subject matter claimed; rather, the description must clearly allow a person of ordinary skill in the art to recognize that he or she invented what is claimed. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991). The test is whether the originally filed specification reasonably conveys to a person having ordinary skill in the art that applicant had possession of the subject matter later claimed. In re Kaslow, 217 USPQ 1089 (Fed. Cir. 1991). Moreover, in order to have possession of members of a claimed genus, the specification need not describe all of the species that the genus encompasses. Amgen Inc. v. Chugai Pharmaceutical Co., 18 USPQ2d 1016, 1027 (Fed. Cir. 1991).

Applicants claim 105 is now directed to a fusion protein comprising at least a portion of a filamentous phage coat protein fused to a binding polypeptide comprising a heavy chain variable domain comprising a CDRH3 scaffold comprising: a) an N-terminal portion of 1 to 4 amino acids in which some or all amino acid positions are structural; b) a C terminal portion of 1 to 6 amino acids in which some or all amino acid positions are structural, and c)a central portion or loop of 1 to 20 contiguous amino acids that can vary in sequence and in length, wherein the portion of the phage coat protein provides for display of the fusion protein on the filamentous phage.

On page 3 of the Office Action, the Examiner contends that the support for a "N-terminal portion of about 1 to 4 amino acids in which some or all amino acid positions are structural" and "a C terminal portion of about 1 to 6 amino acids in which some or all amino acid positions are structural" are not disclosed in the earlier applications. As we understand it, the examiner is raising an issue with respect to the term "about" based on the emphasis placed on those words at page 4 of the Office Action. While not acquiescing to the rejection and solely to expedite prosecution, Applicants claims no longer recite "about".

As discussed previously, Applicants submit that the priority documents disclose the currently claimed subject matter. Applicants direct the Examiner's attention to Figures 45 and 46 of the provisional 60/441,059 (filed January 16, 2003). In addition, many other portions of the

specification provide support including at page 18 of the provisional 60/441,059 (filed January 16, 2003):

> "In one embodiment, structural amino acid positions in a CDRH3 are typically located near the N and C terminus of the CDRH3. Structural amino acid positions are selected from the group consisting of the first N-terminal amino acid, the second N-terminal amino acid and **at least one of the last 6 amino acids at the C-terminus of a heavy chain CDRH3**. In another embodiment, at least one structural amino acid position is one or both of the first two amino acid positions at the N-terminus of a heavy chain CDRH3. In another embodiment, **said at least one structural amino acid position is a third and/or fourth amino acid position from the C-terminus**."
>
> At page 21:
> "A library of randomly generated 17 amino acid CDRH3 indicated that a consensus sequence R-L-R at the N-terminus may be preferred for some embodiments."
>
> The examples indicate at page 107:
>
> "Finally, we combined the above two analysis, positional and by residue type, to determine those amino acids and those positions which were significantly over represented (Figure 45). Positions 96(Arg), 97(Leu), 99(Arg),102a (Gly), 102b (Gly), **102e(Trp), 102f(Phe), 102h(Val), and 102j (Val)** show a significant deviation from random (one and a half standard deviations or greater) for both preference of amino acid type at that position and bias for that position for any given residue as compared to the distribution of that amino acid along the entire 17 residue loop. These amino acid preferences indicate that certain amino acids are preferred at these positions, and that these positions are more likely to play a structural role in CDRH3."

Applicants submit that these passages as well as figures 45 and 46 provide for support and priority for claim 105. It is clear that the specification of the priority document describes a CDRH3 phage coat protein fusion protein (see underline) comprising a " N terminal portion of about 1 to 4 amino acids in which some or all amino acid positions are structural". Please see underlined sections above and Figures 45 and 46. It is also clear that the specification of the priority document also describes and supports a "C terminal portion of about 1 to 6 amino acids in which some or all of the amino acid positions are structural". See bold sections above. Applicants respectfully request acknowledgement of priority of the currently pending claims to provisional application 60/441,059 filed January 16, 2003.

Moreover, similar support can be found in the provisional application 60/488,610 filed July 18, 2003. For example, at page 18 of the provisional, the application states:

"In one embodiment, structural amino acid positions in a CDRH3 are located near the N and C terminus of the CDRH3. For example, in a 17 amino acid CDRH3 region, structural amino acid positions are selected from the group consisting of the first N-terminal amino acid, the second N-terminal amino acid, **at least one of the last 6 amino acids at the C-terminus of a heavy chain CDRH3 or mixtures thereof.** In another embodiment, at least one structural amino acid position is one or both of the first two amino acid positions at the N-terminus of a heavy chain CDRH3. In another embodiment, **said at least one structural amino acid position is a third , fourth and/or sixth amino acid position from the C-terminus."**

At page 22,

"Another embodiment of a CDRH3 region comprises an amino acid sequence R-L/I/M-A_3-R-$(A_5)_n$, wherein A_3 and A_5 are any naturally occurring amino acid and n is 1 to 20. A library of randomly generated 17 amino acid CDRH3 indicated that a consensus sequence R-L/I/M- A_3-R at the N-terminus may be preferred for some embodiments."

At page 109,

"Amino acids that deviated most significantly from random ($p<0.05$) showed a strong selection bias for particular amino acids at certain positions in the CDRH3 peptide. The N terminal end of the peptide was biased towards the sequence motif R(L/I/M)XR. Near the central portion of the peptide, the preference seemed to be for either glycine or hydrophilic residues. The C-terminal end of CDR3 (positions 102e-102j) was characterized by an over representation of hydrophobes (Phe, Val, Ile and Trp) at particular positions."

At page 113,

"These results indicate that amino acids located at the N and C-terminus of CDRH3 should be less diversified than other amino acids. Structural amino acid positions were identified as those positions that had a ratio of wild type amino acid to alanine of at least about 3 to 1 or greater and more preferably, about 10 to 1 or greater. The structural amino acid positions identified in the analysis include the first two N-terminal amino acid positions (positions 96 and 97 in this example) and **one or more of the last 6 amino acid positions located at the C-terminus in the 17 amino acid peptide of CDRH3 (positions 102e, 102f, 102g, 102h, 102i and 102j).**"

Applicants submit that these passages as well as figure 45 provide for support and priority for claim 105. It is clear that the specification of the priority document describes a CDRH3 phage coat protein fusion protein comprising an "N terminal portion of about 1 to 4 amino acids in which some or all amino acid positions are structural". Please see underlined sections above and Figure 45. It is also clear that the specification of the priority document also describes and

supports a "C terminal portion of about 1 to 6 amino acids in which some or all of the amino acid positions are structural". See bold sections above. Applicants request acknowledgement of priority of the currently pending claims to provisional application 60/488,610 filed July 18, 2003.

The Examiner also contends that "at least a portion of a phage coat protein" lacks support in the priority documents. The examiner contends that " a portion of the phage coat protein" reads on a single amino acid and further that the phage coat protein is essential material. Applicants disagree.

While not acquiescing to the rejection and solely to expedite prosecution, Applicants have amended claim 105 to refer to filamentous phage coat protein and wherein the portion of the phage coat protein provides for display of the fusion protein on the filamentous phage. The support for this amendment in the priority document, provisional 60/441,059 (filed January 16, 2003), is found throughout the specification including at page 33, lines 19-31:

> "Phage display" is a technique by which variant polypeptides are displayed as fusion proteins to a coat protein on the surface of phage, *e.g.*, filamentous phage, particles. A utility of phage display lies in the fact that large libraries of randomized protein variants can be rapidly and efficiently sorted for those sequences that bind to a target molecule with high affinity. Display of peptide and protein libraries on phage has been used for screening millions of polypeptides for ones with specific binding properties. Polyvalent phage display methods have been used for displaying small random peptides and small proteins through fusions to either gene III or gene VIII of filamentous phage. Wells and Lowman, *Curr. Opin. Struct. Biol.,* 3:355-362 (1992), and references cited therein. In monovalent phage display, a protein or peptide library is fused to a gene III or a portion thereof, and expressed at low levels in the presence of wild type gene III protein so that phage particles display one copy or none of the fusion proteins.

At page 68, lines 11-16:

> "Examples of viral coat proteins include infectivity protein PIII, major coat protein PVIII, p3, Soc, Hoc, gpD (of bacteriophage lambda), minor bacteriophage coat protein 6 (pVI) (filamentous phage; J Immunol Methods. 1999 Dec 10;231(1-2):39-51), variants of the M13 bacteriophage major coat protein (P8) (Protein Sci 2000 Apr; 9(4):647-54). The fusion protein can be displayed on the surface of a phage and suitable phage systems include M13KO7 helper phage, M13R408, M13-VCS, and Phi X 174, pJuFo phage system (J Virol. 2001 Aug; 75(15):7107-13.v), hyperphage (Nat Biotechnol. 2001 Jan; 19(1):75-8)."

Applicants submit that the portion of the filamentous phage coat protein is not essential material as the sequences and the portions of phage coat proteins that provide for phage

display are known to those of skill in the art and are available in publicly available databases. Applicants provide one such reference attached hereto. In addition, Applicants have provided publicly available references as described above. In addition, Applicants' specification provides the nucleic acid sequence of a portion of the M13 p3 phage coat protein in Figures 15, 16, 17, and 18. For example, in Figure 15, the start of p3 is at nucleotide 965 and the end is shown at nucleotide 1439. This corresponds to about 158 amino acids of the C terminal end of the p3 protein as described at page 99, lines 10-15:

> "Vectors encoding fusion polypeptides comprising variant CDRs were constructed as follows. In general, vectors for antibody phage display were constructed by modifying vector pS1602 (Sidhu et al., J. Mol. Biol. (2000), 296:487-495). Vector pS1602, which has pTac promoter sequence and *malE* secretion signal sequence, contained a sequence of human growth hormone fused to the C-terminal domain of the gene-3 minor coat protein (p3)."

Applicants submit that they have sufficiently described the portion of phage coat proteins by providing publicly available sources for the sequences of the phage coat proteins, and describing at least one embodiment of the C terminal portion of the M13 p3 protein. As the Board of Appeals indicated in Ex parte Rios at page 7,

> "[W]hat is needed to support generic claims to biological subject matter depends on a variety of factors , such as existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, the predictability of the aspect at issue, and other considerations appropriate to the subject matter..."

Applicants submit that the Examiner has not provided any evidence that one of skill in the art would not have been in possession of at least a portion of a phage coat protein given the disclosure in the specification as well as the knowledge in the art.

In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of the objection to the claim to priority.

Rejection under 35 U.S.C. § 102(a)

The Examiner rejects claims 105-107, 109, 111, 113, and 115-128 under 35 U.S.C. § 102(a) as allegedly anticipated by Bond et al. (*J. Mol. Biol.*, 332:643-655 (2003)). Applicant respectfully traverses this rejection.

Applicants submit that the pending claims are entitled to a priority date of at least Jan. 16, 2003 and July 18, 2003 (see argument above). The Bond et al. paper was published on

September 19, 2003, and Applicant respectfully asserts that it is therefore not properly considered prior art to the instant application.

Applicant respectfully requests removal of the rejection under 35 U.S.C. § 102(a).

Rejection under 35 U.S.C. § 112, First Paragraph

The Examiner rejects claims 105-107, 109-111, and 113-128 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The Examiner contends that the rejected limitations are new matter. The examiner contends that there is no support for a portion of a phage coat protein, for a hydrophobic amino acid residue at position 45, and no support for two framework regions. Applicants respectfully traverse.

Under 35 U.S.C. §112, first paragraph, a patent specification must contain sufficient written description in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention (*Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991)). "The specification must teach the invention by describing it." (*Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 926 (Fed. Cir. 2004)).

At least a portion of a phage coat protein. The Examiner rejects claim 105 for reciting "at least a portion of a phage coat protein". Applicant respectfully asserts that "at least a portion of a phage coat protein" is described throughout the specification, including at page 11, lines 3-4; page 18, lines 8-9; page 55, line 28 to page 56, line 6; page 88, lines 12-13; and page 99, lines 29-31. At page 100, lines 5-15, the specification provides further description.

> [A] fusion protein comprises an antibody variable domain...fused to all or a portion of a viral coat protein. Examples of viral coat proteins include infectivity protein PIII, major coat protein PVIII, p3, Soc, Hoc, gpD (of bacteriophage lambda), minor bacteriophage coat protein 6 (pVI) (filamentous phage; J Immunol Methods. Dec. 10, 1999;231(1-2):39-51), variants of the M13 bacteriophage major coat protein (P8) (Protein Sci April 2000; 9(4):647-54). The fusion protein can be displayed on the surface of a phage and suitable phage systems include M13KO7 helper phage, M13R408, M13-VCS, and Phi X 174, pJuFo phage system (J Virol. August 2001; 75(15):7107-13.v), hyperphage (Nat Biotechnol. January 2001; 19(1):75-8). The preferred helper phage is M13KO7, and the preferred coat protein is the M13 Phage gene III coat protein.

Applicants submit that the portion of the filamentous phage coat protein is described in the specification and are known to those of skill in the art as the sequences and the portions of phage coat proteins that provide for phage display are available in publicly available databases. Applicants provide one such reference attached hereto. In addition, Applicants have provided publicly available references as described above. The working examples provide detailed description of fusion proteins as well as how to make a fusion protein comprising at least a portion of a phage coat protein.

In addition, Applicants' specification provides the nucleic acid sequence of a portion of the M13 p3 phage coat protein in Figures 15, 16, 17, and 18. For example, in Figure 15, the start of p3 is at nucleotide 965 and the end is shown at nucleotide 1439. This corresponds to about 158 amino acids of the C terminal end of the p3 protein as described at page 99, lines 10-15:

> "Vectors encoding fusion polypeptides comprising variant CDRs were constructed as follows. In general, vectors for antibody phage display were constructed by modifying vector pS1602 (Sidhu et al., J. Mol. Biol. (2000), 296:487-495). Vector pS1602, which has pTac promoter sequence and *malE* secretion signal sequence, contained a sequence of human growth hormone fused to the C-terminal domain of the gene-3 minor coat protein (p3)."

Applicants submit that they have sufficiently described the portion of phage coat proteins by providing publicly available sources for the sequences of the phage coat proteins, and describing at least one embodiment of the C terminal portion of the M13 p3 protein. As the Board of Appeals indicated in Ex parte Rios at page 7,

> "[W]hat is needed to support generic claims to biological subject matter depends on a variety of factors , such as existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, the predictability of the aspect at issue, and other considerations appropriate to the subject matter..."

Applicants submit that the Examiner has not provided any evidence that one of skill in the art would not have been in possession of at least a portion of a phage coat protein given the disclosure in the specification as well as the knowledge in the art. For at least this reason, Applicant respectfully asserts that the specification fully describes "at least a portion of a phage coat protein."

Any hydrophobic amino acid. The Examiner rejects claim 123 and alleges that the "residue at framework position 45 may be any hydrophobic amino acid" lacks written description. Applicant respectfully traverses.

The specification supports the recitation of framework position 45 being wild-type arginine or any hydrophobic amino acid. Specifically, support for this claim can be found in Example 14 at pages 163-164 of the specification and in Figure 40. Figure 40 shows the preference for hydrophobic amino acids at that position including phe, leu, trp, val, met and tyr. At page 86, line 30 to page 87, line 5, the specification states:

> "The hydrophobic amino acids are preferably selected from the group consisting of leucine, isoleucine, valine, tryptophan, tyrosine, and phenylalanine. In a VHH variable domain, the structural amino acids positions in a CDRH3 are preferably substituted with hydrophobic amino acids to stabilize the VHH in the absence of the light chain at the former light chain interface."

The specification at page 163, line 31 to page 164, line 4 recites:

> Aside from Arg, **both domains preferred hydrophobic residues at position 45 and** the RIG domain in particular contained a substantial proportion of Trp, Phe and Leu residues. Overall, these results demonstrate that changes at positions 37 and 45 of V_HH domains relative to V_H domains contribute to protein stability, as they allow for favorable hydrophobic interactions amongst themselves and with CDR3. See Figure 52. emphasis added

For at least this reason, Applicant respectfully asserts that "any hydrophobic amino acid" at framework region position 45 is fully described by the specification.

Another framework region. The Examiner rejects claim 126 due to the recitation of "another framework region." Applicant respectfully traverses.

Claim 123 recites "a framework region that comprises a hydrophobic amino acid at position 37 and an amino acid at position 45 selected from..." Claim 26 depends on claim 123 and recites "wherein the antibody heavy chain variable domain further comprises another framework region, wherein the another framework region comprises an amino acid at amino acid position 91..." This claim has express support in Example 7 at page 141, line 30 to page 142, line 17. Example 7 discloses a library of monobodies where four variants were generated at four framework positions—residues 37, 45, 47, and 91. These residues are the ones particularly claimed in claims 123 and 126. Residues 37, 45, and 47 are in Framework Region 2 and residue 91 is in Framework Region 3 with CDRH2 positioned between the two framework regions.

Thereby, framework region 3 is the "another framework." Framework regions of antibodies are known to those of skill in the art and sequences for the framework regions are publicly available. For at least this reason, Applicant respectfully asserts that "another framework region" is fully supported by the specification.

The examiner has not provided any evidence that one of skill in the art would not have been in possession of at least two framework regions given the disclosure in the specification as well as the knowledge in the art. In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of the rejections under 5 U.S.C. § 112, first paragraph.

Rejection under Obviousness-Type Double Patenting

The Examiner provisionally rejects claims 105, 107, 109, 111, 113, 115-122 and 127-128 under the judicially created doctrine of obviousness-type double patenting over claims 22, 25, 26, 30-31, 35-37 and 48-50 of copending Application No. 11/102,502 in view of Sidhu et al. (*J. Mol. Biol.,* 296:487-495 (2000)) and evidenced by Bond et al. (*J. Mol. Biol.,* 332:643-655 (2003)). Applicant acknowledges the Examiner's rejection for obviousness-type double patenting and requests that this rejection be held in abeyance until notice of allowable subject matter.

Interview Request

Applicants request an interview with the examiner and her supervisor upon receipt of these papers.

Summary

Applicant submits that the claims of the present application are in condition for allowance and notification to that effect is earnestly solicited. The Examiner is invited to contact Applicant's representative at the telephone number listed below, if the Examiner believes that doing so will advance prosecution.

Please charge any additional fees or credit any overpayment to Merchant & Gould P.C., Deposit Account No. 13-2725.

Respectfully submitted,

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Date: June 15, 2009

/Brian R. Dorn/
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